UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
08/249,689	05/26/1994	PAUL R. SCHIMMEL	MIT5261	9517

23579 7590 12/23/2005

PATREA L. PABST
PABST PATENT GROUP LLP
400 COLONY SQUARE
SUITE 1200
ATLANTA, GA 30361

EXAMINER	
BRUSCA, JOHN S	

ART UNIT	PAPER NUMBER
1631	

DATE MAILED: 12/23/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Response to Remand to Examiner in Application No. 08/249689 by the Board of Patent Appeals and Interferences, mail date 19 September 2005

The Board of Patent Appeals and Interferences issued a remand in this application to the examiner after consideration of a request for rehearing of the decision by the Board, mail date 30 October 2003. In the Board decision, a rejection under 35 U.S.C. § 112, first paragraph for lack of written description was reversed concerning claims drawn to products that bind the minor groove of the acceptor stem of tRNA and inhibit the function of the tRNA. In the remand the Board requested additional discussion of issues of record. In particular the Board requested a comparison of the facts of the instant application with that of Univ. of Rochester v. G.D. Searle & Co., 69 USPQ2d 1886 (CAFC 2004).

It is noted that the Remand filed by the Board on 19 September 2005 does not reflect the amendment entered 24 December 2003 in which claims 12 and 17 were cancelled and claims 11, 18, and 19 were amended. The pending claims rejected for lack of written description are 11, 13, 18, 19, and 21.

In an attempt to thoroughly respond to the issues discussed in the remand, the application file has been reviewed. Detailed below are clarifications of several points made by the Office during prosecution of the instant application.

35 U.S.C. 112, first paragraph states that "The specification shall contain a written description of the invention." This requirement cannot be satisfied by showing that post filing art describes the invention, or that the specification enables to make and use the invention.

On page 3 of the appeal brief filed 16 September 2002 the appellants noted a reduction to practice on pages 31-33 and page 36, however the sections pointed to merely show that

mutations in the stem region of a tRNA inhibit the function of the tRNA molecules. The section pointed to therefore shows a possible critical region in a functional tRNA that could be targeted by a compound, but does not reduce to practice the claimed compounds. That is, there is no written description of any chemical structure(s) which have the function of being inhibitory to the targeted critical region.

The declarations of Julius Rebek Jr. and James R. Williamson filed 11 April 2002 discuss the minor groove of tRNA. The declarations discuss possible interactions with a hypothetical compound that binds a minor groove of tRNA including hydrophobic interactions, hydrogen bonds, electrostatic interactions, and steric constraints. The declarations discuss methods of computer modeling of hypothetical compounds that could bind to a minor groove of tRNA. The declarations analogize design of the claimed compounds with a lock and key, however, as previously noted in the Examiner's Answer mailed 02 January 2003, design of locks and keys are different than design of chemical compounds. If the analogy must be pursued, however, then the instant claims are analogous to an application that claims a lock (comprising mechanically complicated structures), but only describes a key. Description of a key does not describe the details of a lock with which the key interacts. The Williamson declaration discusses compounds that bind the minor groove of **DNA** and a ribosomal protein that binds to **ribosomal RNA** but does not discuss examples of compounds that bind to **tRNA**. It is noted that the claimed compounds do not merely bind to a critical site, but must also inhibit the function of a tRNA. Neither declaration addresses the limitation of inhibition of function of a tRNA in their discussion of design of the claimed compounds. The declarations do not present any objective evidence that the instant specification describes the claimed compounds. The evidence presented

in the declarations is relevant to whether one of skill in the art would be enabled to make and use a compound that binds to the minor groove of a tRNA, rather than whether the claimed compounds are described. It is noted that both declarations express a legal opinion that the claimed compounds are described, but as noted below, the MPEP states at 716.01(b) that opinion evidence is not given any weight.

OPINION EVIDENCE

Although factual evidence is preferable to opinion testimony, such testimony is entitled to consideration and some weight so long as the opinion is not on the ultimate legal conclusion at issue. While an opinion as to a legal conclusion is not entitled to any weight, the underlying basis for the opinion may be persuasive. In re Chilowsky, 306 F.2d 908,134 USPQ 515 (CCPA 1962) (expert opinion that an application meets the requirements of 35 U.S.C. 112 is not entitled to any weight; however, facts supporting a basis for deciding that the specification complies with 35 U.S.C. 112 are entitled to some weight); In re Lindell, 385 F.2d 453, 155 USPQ 521 (CCPA 1967) (Although an affiant's or declarant's opinion on the ultimate legal issue is not evidence in the case, "some weight ought to be given to a persuasively supported statement of one skilled in the art on what was not obvious to him." 385 F.2d at 456, 155 USPQ at 524 (emphasis in original)). In assessing the probative value of an expert opinion, the examiner must consider the nature of the matter sought to be established, the strength of any opposing evidence, the interest of the expert in the outcome of the case, and the presence or absence of factual support for the expert's opinion. Ashland Oil, Inc. v. Delta Resins & Refractories, Inc., 776 F.2d 281, 227 USPQ 657 (Fed. Cir. 1985), cert. denied, 475 U.S. 1017 (1986). See also In re Oelrich, 579 F.2d 86, 198 USPQ 210 (CCPA 1978) (factually based expert opinions on the level of ordinary skill in the art were sufficient to rebut the prima facie case of obviousness); Ex parte Gray, 10 USPQ2d 1922 (Bd. Pat. App. & Inter. 1989) (statement in publication dismissing the "preliminary identification of a human b-NGF-like molecule" in the prior art, even if considered to be an expert opinion, was inadequate to overcome the rejection based on that prior art because there was no factual evidence supporting the statement); In re Carroll, 601 F.2d 1184, 202 USPQ 571 (CCPA 1979) (expert opinion on what the prior art taught, supported by documentary evidence and formulated prior to the making of the claimed invention, received considerable deference); In re Beattie, 974 F.2d 1309, 24 USPQ2d 1040 (Fed. Cir. 1992) (declarations of seven

persons skilled in the art offering opinion evidence praising the merits of the claimed invention were found to have little value because of a lack of factual support); Ex parte George, 21 USPQ2d 1058 (Bd. Pat. App. & Inter. 1991) (conclusory statements that results were "unexpected," unsupported by objective factual evidence, were considered but were not found to be of substantial evidentiary value).

On page 7 of the appellant's reply brief filed 03 March 2003 the appellants state that the structure of the claimed compounds are defined by their interactions with the target site on the stem of tRNA. However the claims are drawn to compounds that are **functionally** defined by the ability to bind to the minor groove of the acceptor stem of a tRNA in claims 11, 13, and further limited to a target of $tRNA^{Ala}$ in claim 18, a target of G3:U70 in the stem in claim 19, and a compound that is a nucleic acid in claim 21. It is further noted that the genus of critical sites that allows for inhibition of tRNA function when bound by the claimed compounds of claims 1, 13, 18, and 21 is not described. Although conserved structures of tRNA acceptor stems are described, there is no description of which sites in the acceptor stem allow for inhibition of function when bound by the claimed compound. Claim 19 is limited to one site of an acceptor stem, however the specification only shows that mutations in the site of claim 19 results in inhibition of tRNA function, which does not equate to a description of a wild type site that inhibits tRNA function when bound by the compound of claim 19. The appellants do not explain how knowledge of a binding site on a target leads to description of the structure of a compound that binds the target. Although a binding site comprises a number of chemical groups that can form hydrogen bonds, hydrophobic interactions, electrostatic interactions, and further provides steric constraints to a compound that binds the binding site, these constraints provide little correlation with the overall structure of a compound that binds the binding site. Many polar chemical groups in a compound can form hydrogen bonds, many nonpolar chemical groups can

form hydrophobic interactions, many charged chemical groups can form electrostatic interactions, and many compounds are able to fit within the steric constraints of the binding site. What is missing from the description is the structure of a compound that combines and properly orients the chemical groups required to bind the minor groove of a tRNA acceptor stem and inhibit the function of the tRNA. The Board noted this point in their decision mailed 30 October 2003 in the instant application (regarding claims 11-13 and 21 prior to the amendment of 24 December 2003 in which claims were limited to a target of tRNA acceptor stem) as follows:

Appellant argues that the hydrogen bond donor and acceptor sites are structural features tied to function, but merely stating that an unspecified compound has an arrangement of hydrogen bond donor and acceptor sites that allows the compound to bind a critical site in the minor groove of an unspecified RNA target molecule and inhibit RNA function does nothing to allow one skilled in the art to visualize or recognize the identity of the members of the genus. It may define a desirable result, but it does not define the inhibitor that achieves that result. That the "lock and key" mechanism of RNA inhibition may be analogous to the mechanism of antibody-antigen recognition is beside the point.

The Board's reasoning is equally applicable to a binding site that is limited to a tRNA acceptor stem. The only aspect of the claimed compounds that is described is the function of binding to the claimed binding site. The description of the claimed compounds ends at the interface of the binding site and the claimed compounds.

Compounds whose structure is not described may instead be described by other physical characteristics and by a known relation between a described function and structure. Antibodies that specifically bind an antigen may be described by description of the antigen in view of the relationship between the structure of an antigen and an antibody to which it binds. The structure of an antigen not only determines aspects of the binding pocket of its corresponding antibody,

but possession of an antigen allows for assured possession of its corresponding antibody through well recognized methods of obtaining the corresponding antibody without requiring knowledge of the structure of the antibody. In Noelle v. Lederman 69 USPQ2d 1508 (CAFC 2004), the CAFC ruled that an antibody to human CD40CR antigen was not adequately described in an application for which priority was claimed because the claimed application did not adequately describe the human antigen. Instead, the claimed application described only mouse CD40CR antigen. The CAFC stated that if the human antigen had been described in the claimed application, then the antibody to the human antigen would also have been adequately described.

In pages 19-23 of the appellant's brief filed 16 September 2002 the appellants analogize written description of antigens and antibodies to that of the claimed invention. The appellants state that the critical region of the RNA is analogous to an isolated and described antigen, and the claimed compounds are analogous to an antibody that binds a described antigen. The analogy is inaccurate because although some constraints on the structure of the claimed compound are imposed by the critical site on the tRNA to which it binds, the claimed compound does not have a recognized conserved structure, nor is there a method of obtaining the claimed compound that is so direct and recognized that possession of the critical site equates to possession of the claimed compound. The only method of obtaining the claimed compound described is by the method of step (e) of instant claim 1, which although enabled, requires considerable trial and error computational experimentation with unpredictable results. There is no known or disclosed correlation between the claimed function of the claimed compounds and their structure.

In pages 6-7 of the Remand mailed 19 September 2005, the Board notes Example 16 of the USPTO Synopsis of Application of Written Description Guidelines which deals with written

description of antibodies that specifically bind a described antigen. The example states a number of reasons why the antibody should be considered as described. The reasons are contrasted with the instant facts as follows:

1) There is a routine art-recognized method of making antibodies to fully characterized antigens. In contrast although there is a prior art method of designing compounds that bind to a target molecule, there is no prior art method of making the specifically claimed compounds.

2) There are well-defined structural characteristics for the five classes of antibody. In contrast there are no examples of the claimed compounds in the instant specification or the prior art.

3) The functional characteristics of antibody binding. It is assumed that this refers to the conserved structural-functional properties of antibody binding sites. In contrast the claimed compounds are defined only functionally by their ability to bind to a critical site and inhibit function of a tRNA.

4) Antibody technology is well developed and mature. In contrast the methods of making the claimed compounds requires computational experimentation to design compounds with unpredictable results, and further would require experimental testing to determine if proposed structures inhibit the function of a tRNA molecule.

In University of Rochester v. G.D. Searle & Co., 69 USPQ2d 1886 (CAFC 2004) the CAFC ruled that claims drawn to methods of using a COX-2 inhibitor were not described in view of a description of a screening method for COX-2 inhibitors and the absence of description of the inhibitors themselves. COX-2 is an enzyme known as a cyclooxygenase whose metabolic products result in inflammation. Regarding description in different fact situations, the CAFC

contrasts description of polynucleotides and description of the general class of chemical compounds at page 1894:

We agree with Rochester that *Fiers*, *Lilly*, and *Enzo* differ from this case in that they all related to genetic material whereas this case does not, but we find that distinction to be unhelpful to Rochester's position. It is irrelevant; the statute applies to all types of inventions. We see no reason for the rule to be any different when non-genetic materials are at issue; in fact, where there might be some basis for finding a written description requirement to be satisfied in a genetics case based on the complementariness of a nucleic acid and, for example, a protein, that correspondence might be less clear in a non-genetic situation. In *Enzo*, we explained that functional descriptions of genetic material can, in some cases, meet the written description requirement if those functional characteristics are "coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics."323 F.3d at 964 (quoting from the PTO's *Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, P1, "Written Description" Requirement*, 66 Fed. Reg. 1099, 1106). DNA and RNA are each made up of just four building blocks that interact with each other in a highly predictable manner. Each of those building blocks, or "nucleotides," is characterized by a unique "base": In the case of DNA, the four nucleotides include the bases adenine, thymine, cytosine, and guanine; RNA also includes adenine, cytosine, and guanine, but contains the base uracil in place of thymine. Adenine on one strand of DNA binds, or "hybridizes," to thymine on the other; in RNA, adenine binds to uracil; and in either DNA or RNA, cytosine binds to guanine. Given the sequence of a single strand of DNA or RNA, it may therefore have become a routine matter to envision the precise sequence of a "complementary" strand that will bind to it. Therefore, disclosure of a DNA sequence might support a claim to the complementary molecules that can hybridize to it.

The same is not necessarily true in the chemical arts more generally. Even with the three-dimensional structures of enzymes such as COX-1 and COX-2 in hand, it may even now not be within the ordinary skill in the art to predict what compounds might bind to and inhibit them, let alone have been within the purview of one of ordinary skill in the art in the 1993-1995 period in which the applications that led to the '850 patent were filed. Rochester and its experts do not offer any persuasive evidence to the contrary. As the district court pointed out:

Tellingly, ... what plaintiff's experts'[sic] do *not* say is that one of skill in the art would, from reading the patent, understand what compound or compounds—which, as the patent makes clear, are necessary to practice the claimed method—would be suitable, nor would one know how to find such a compound except through trial and error ... . Plaintiff's experts opine that a person of ordinary skill in the art would understand from reading the '850 patent what method is claimed, but it is clear from reading the patent that one critical aspect of the method—a compound that selectively inhibits PGHS-2 activity—was hypothetical, for it is clear that the inventors had neither possession nor knowledge of such a compound.

Univ. of Rochester, 249 F. Supp. 2d at 229

Thus the CAFC stated that chemical compounds generally require more description than merely binding specificity. Because University of Rochester concerns description of a claimed method of using a compound that binds to and inhibits an enzyme it is more relevant to the instant fact situation than the antigen-antibody situation discussed above.

In the response to the request for reconsideration filed by the appellants on 24 November 2004, the appellants state on page 14 that the claimed compounds could be obtained without undue experimentation, however the rejection is based not on an enablement standard, but rather on a written description standard. The appellants have not shown how the instant claimed compounds are any better described than the COX-2 inhibitors in Rochester.

In the remand filed by the Board 19 September 2005, the Board notes some differences between the fact situation of Rochester and the instant application. The Board correctly states that in Rochester a critical site was not shown. In Rochester the patent described a bioassay for screening compounds to determine if the compounds inhibited COX-2 activity. It is clear that for COX-2 inhibitors to inhibit the target enzyme, the inhibitor must bind a site in the enzyme. In the Rochester decision, the CAFC did not state whether description of a binding site was relevant to description of COX-2 inhibitors. The CAFC focused on the lack of description of the

structure of the inhibitors and the lack of a known correlation between function and structure. The CAFC did state that knowledge of the three-dimensional structure of the enzyme target would not likely serve to describe the inhibitors of the enzyme (see the passage quoted above). It is further noted that instant claims 11, 13, 18, and 21 are drawn to compounds that bind to a genus of critical sites that is not adequately described, because only the critical site of claim 19 is specifically described, and it is not apparent from the specification that even the critical site of claim 19 is an operative embodiment, as noted above. The Board notes the appellant's assertions and declarations that suggest that knowledge of the structure of the critical site of the tRNA equates with knowledge of the structure of the claimed compounds. As discussed above, knowledge of the structure of a binding site is merely a starting point on a research project to develop the claimed compounds. The declarations of Rebek and Williamson do not show that one skilled in the art would believe that appellant had possession of the claimed compounds based on knowledge of a binding site. Finally, the Board notes that even antibodies that bind a described antigen have unpredictable structures in their binding sites. Nevertheless, the CAFC has ruled in Noelle that description of the structure of an antigen is sufficient to describe the corresponding antibody that binds the antigen. The CAFC has not extended that logic to other fact situations, and in Rochester it is plain that the CAFC position is that without a known correlation between function and structure, a functional description of a chemical compound is presumed to be inadequate to meet the written description requirement of 35 U.S.C. § 112, first paragraph.

John S. Bruska 22 December 2005

JOHN S. BRUSCA, PH.D
PRIMARY EXAMINER